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TOPIC HIGHLIGHT

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Nutrition and exercise in the management of liver cirrhosis

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Abstract

Liver cirrhosis (LC) patients often have protein-energy malnutrition (PEM) and decreased physical activity. These conditions often lead to sarcopenia, which is the loss of skeletal muscle volume and increased muscle weakness. Recent studies have demonstrated that PEM and sarcopenia are predictors for poor survival in LC patients. Nutrition and exercise management can improve PEM and sarcopenia in those patients. Nutrition management includes sufficient dietary intake and improved nutrient metabolism. With the current high prevalence of obesity, the number of obese LC patients has increased, and restriction of excessive caloric intake without the exacerbation of impaired nutrient metabolism is required for such patients. Branched chain amino acids are good candidates for supplemental nutrients for both obese and non-obese LC patients. Exercise management can increase skeletal muscle volume and strength and improve insulin resistance; however, nutritional status and LC complications should be assessed before an exercise management regimen is implemented in LC patients. The establishment of optimal exercise regimens for LC patients is currently required. In this review, we describe nutritional status and its clinical impact on the outcomes of LC patients and discuss general nutrition and exercise management in LC patients.

Key words: Liver cirrhosis; Protein-energy malnutrition; Sarcopenia; Obesity; Exercise

Core tip: Recent studies have shown that sarcopenia is a predictor of poor survival in liver cirrhosis (LC) patients. LC-associated sarcopenia develops based on impaired nutrient metabolism and decreased physical activity. To improve this condition, nutrition and exercise management is imperative. Energy intake with branched chain amino acid supplementation is a promising method for nutrition management. Exercise can increase skeletal muscle volume and strength; however, nutritional status and LC complications should be assessed before exercise management begins. Obesity is another health issue for LC patients; improvement of insulin resistance is a key component in nutrition and exercise management for obese LC patients.

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INTRODUCTION

Liver cirrhosis (LC) is a critical stage of chronic liver disease with poor outcomes. Substantial data have indicated that poor liver function and the occurrence of hepatocellular carcinoma (HCC) are responsible for the shortened survival of LC patients[1-4]. Accumulating data have also demonstrated that LC patients often develop protein-energy malnutrition (PEM) at a rate of 25.1%-65.5%[5-8] and that PEM plays a crucial role in their poor survival[6,9-11].

LC-associated PEM occurs in combination with poor dietary intake, malabsorption, increased intestinal protein loss, decreased hepatic protein synthesis, abnormal substrate utilization, and hypermetabolism[12,13]. Individuals with PEM typically suffer from a loss of skeletal muscle volume and from muscle weakness; this condition is classified as sarcopenia[14]. Aging-related sarcopenia is defined as primary sarcopenia, while LC is a cause of secondary sarcopenia[15]. Recent studies have demonstrated that sarcopenia is an independent predictor of poor survival in LC patients with or without HCC[16,17]. However, overnutrition is increasingly affecting humans worldwide[18], and thus, overweight/obesity are frequently observed in LC patients. For example, 72.4% of patients had excess caloric intake in a study of compensated hepatitis C virus (HCV)-related LC[19], and 61% of compensated HCV-related LC patients have a body mass index (BMI) $\geqslant$ 25 kg/m^2[20]. Both chronic HCV infection[21] and overweight/obesity can cause insulin resistance, which raises the risk of liver fibrosis progression[22] and HCC occurrence[23] in HCV-related LC. Thus, clinicians are now confronted with problems related to malnutrition and overnutrition in the management of LC. In this review, we describe nutritional status and its clinical impact on the outcomes of LC patients and discuss nutrition and exercise management strategies for LC patients.

ENERGY METABOLISM ASSOCIATED WITH PEM IN LC PATIENTS

Metabolic activity

Metabolic activity can be assessed by comparing a measured resting energy expenditure (REE) and a predicted REE[24]. There are notable differences in metabolic activity among LC patients; previous studies have reported that 15%-33.8% of LC patients exhibited hypermetabolism, while 8%-31% were hypometabolic[7,8,25,26]. Earlier studies with LC patients demonstrated that a hypermetabolic state is strongly associated with decreased muscle volume[27]. Increased beta-adrenergic activity may explain, at least in part, hypermetabolism[26]. In a multicenter prospective study, a detailed analysis of metabolic activity and energy balance in LC patients was conducted. The results showed that PEM significantly correlated with Child-Pugh grade, that hypermetabolic and hypometabolic patients showed a significant decrease in kg of free fat mass, and that hypermetabolic patients had a positive energy balance due to decreased physical activity, while hypometabolic patients had a negative energy balance due to a reduced caloric intake[7].

The relationship between metabolic activity and outcomes in LC patients has been investigated. A study found that survival rate is significantly higher in normal metabolic LC patients than in hypometabolic or hypermetabolic LC patients[10]. Furthermore, some results have suggested that LC-related hypermetabolism is a factor associated with both transplant-free[25,28] and post-transplantation survival[29]. Hypermetabolic LC patients have decreased transplant-free survival compared with non-hypermetabolic LC patients (9.7 mo *vs* 31.8 mo, $P = 0.05$)[28]. Moreover, in a study of patients with end-stage liver disease, pre-transplantation hypermetabolism was associated with decreased post-transplantation survival[29].

Carbohydrate and lipid metabolism

The liver plays a critical role in carbohydrate and lipid metabolism. Ingested carbohydrates are taken up by the liver and converted into and stored as glycogen. In the fasting state, glucose is generated in the liver *via* glycogenolysis and gluconeogenesis; thus, blood glucose levels are maintained[30]. Because LC patients have decreased gluconeogenesis ability and glycogen stores capacity[31], they are prone to entering into a starvation state after a relatively short fasting period (*e.g.*, overnight)[32]. In this situation, lipid metabolism is enhanced; energy metabolism shifts from a carbohydrate preference to lipid oxidation preference[33-35]. Accordingly, free fatty acid (FFA) levels are elevated in LC patients. A previous study found that impaired re-esterification rather than accelerated lipolysis elevates FFA in LC patients[36].

Protein metabolism

Because albumin synthesis is decreased in LC patients, serum albumin levels inversely correlate with the grade of liver dysfunction[37]. Furthermore, in a study of compensated LC patients with alanine aminotransferase levels > 50 IU/L, a positive correlation between serum albumin levels and skeletal muscle volume was observed[38]. LC-associated PEM accelerates protein catabolism, which is the overall breakdown of cellular proteins, mainly in skeletal muscles, and which provides amino acids, especially branched chain amino acids (BCAAs), for protein synthesis and energy supply[39-41]. BCAAs consist of leucine, isoleucine, and valine. In a study with LC patients, energy efficacy (increased energy expenditure/energy equivalent of the supplemented nutrient) was significantly higher in BCAAs (96% ± 16%) than in glucose (96% ± 16% *vs* 41% ± 8%, $P < 0.01$) and fatty acids (96% ± 16% *vs* 27% ± 13%, $P < 0.05$)[42]. Moreover, BCAAs are consumed for ammonia detoxification in LC patients in whom hepatic detoxification to urea is impaired. Skeletal muscles and, to a lesser extent, the brain clear blood ammonia by incorporating ammonia into the process of glutamine production from glutamate. During the process, BCAAs are required for glutamate synthesis[40]. Thus, there is a frequent lack of BCAAs in LC patients, resulting in decreased albumin synthesis. In contrast to decreased BCAA levels, aromatic amino acid (AAA) levels are typically increased in LC patients[43,44], although underlying mechanisms for the altered AAA metabolism in LC are not fully understood. A decrease in the BCAA to AAA ratio (Fischer ratio; BCAA to tyrosine ratio, BTR) is thought to play a causal role in hepatic encephalopathy by enhanced brain AAA uptake and subsequent neurotransmission disturbance[45]. Recent studies have suggested that this amino acid imbalance occurs in the early stages of LC[46].

IMPACT OF SARCOPENIA ON LC PATIENT OUTCOMES

Sarcopenia

As described above, protein breakdown from skeletal muscles is an important pathologic mechanism for sarcopenia in LC patients. Recently, some analyses have indicated that hyperammonemia can cause sarcopenia. The results of an animal experiment demonstrated that skeletal muscle autophagy is induced by hyperammonemia and may contribute to sarcopenia in cases of LC[47]. Another study showed that skeletal muscle from LC patients had increased expression of myostatin, a known inhibitor of skeletal muscle accretion and growth. That study found that myostatin expression is induced by hyperammonemia in murine myotubes, suggesting a mechanism by which sarcopenia develops in LC patients[48].

Recent studies have examined outcomes in LC patients with sarcopenia[16,17]. In a study of LC patients in which sarcopenia was observed in 40% of the patients, sarcopenia, Child-Pugh scores, and model for end-stage liver disease (MELD) scores were each found to be independent factors for mortality, with the mortality risk more than 2-fold higher in sarcopenic than nonsarcopenic patients[16]. Interestingly, the study also revealed a strong relationship between sarcopenia and sepsis-related death, which may reflect the impaired immunity found in LC patients. In line with those findings, a prospective study of LC patients demonstrated that PEM is an independent predictor of bacterial infection[49]. Furthermore, sarcopenia has been shown to correlate with poor survival after liver transplantation[50,51].

Sarcopenic obesity

The current global obesity epidemic has created a new condition: the combination of sarcopenia and obesity, described as sarcopenic obesity[52]. Because LC patients occasionally have sarcopenia (40%)[16] and obesity (30%-31%)[53,54], it can be deduced that a considerable number of them may have sarcopenic obesity. Furthermore, obesity is frequently accompanied by nonalcoholic fatty liver disease (NAFLD), and the prevalence of this liver disease is increasing in industrialized countries[55-57]. NAFLD can progress to nonalcoholic steatohepatitis and LC. Given this global trend, sarcopenic obesity will likely be a major condition in LC patients in the future.

Obesity typically occurs in tandem with decreased physical activity[58,59], which may create a vicious cycle of sarcopenia progression. Obesity also induces insulin resistance and systemic inflammation, both of which prompt hypercatabolism and impair the anabolic effect of muscles, resulting in protein breakdown stimulation and muscle synthesis suppression[59-61]. Moreover, a recent study revealed that sarcopenic obesity is more closely associated with insulin resistance than sarcopenia or obesity alone[62]. Taken together, this new condition appears to accelerate sarcopenia progression.

Although sarcopenia has been reported to be predictive of poor survival in LC patients[16,17], the impact of sarcopenic obesity on LC patient outcomes remains unknown. However, it has been suggested that obesity is an independent predictor of hepatic decompensation in LC patients[53]. Furthermore, obesity has been shown to be a risk factor for LC-related death or hospitalization[63,64]. A study of cancer patients revealed that sarcopenic obesity is associated with a poorer functional status compared with obesity without sarcopenia and is an independent predictor of survival[65]. These findings provide the rationale for further studies to clarify whether sarcopenic obesity worsens LC patient outcomes.

ASSESSMENT METHODS FOR PEM IN LC PATIENTS

Table 1 lists the methods used to assess PEM and sarcopenia.

Indirect calorimetry

Indirect calorimetry can measure oxygen consumption per minute (V_{O_2}) and carbon dioxide production per minute (V_{CO_2}), thus calculating energy expenditure and non-protein respiratory quotient (npRQ). npRQ is considered to be a good marker for PEM assessment. In LC patients, npRQ is lower than in normal controls due to a shift of preferred energy metabolism from carbohydrate to lipid oxidation. A recent study of LC patients has revealed that the survival rate is significantly lower in patients with low npRQ (< 0.85) than in patients with scores above 0.85 ($P < 0.01$)[10]. Although the utility of indirect calorimetry in assessing energy metabolism has been proven, the high cost constrains its clinical application.

Anthropometric measurement

Because skeletal muscle volume reflects nutritional status, anthropometric measurement has been conducted to assess PEM in LC patients[66,67]. PEM indices include triceps skinfold thickness (TSF), arm muscle circumference (AMC), and arm circumference (AC). A study with LC patients reported that decreased AMC and TSF correlate with malnutrition and decreased liver functional reserve[67]. Accumulated data found a significant association between nutritional status estimated by anthropometric measurement and outcomes in LC patients. A previous study suggested that AMC may improve the prognostic capacity of Child-Pugh scores in LC patients[68]. Another study demonstrated that AMC and TSF may be useful in predicting survival of LC patients. In addition, the prognostic power of AMC was found to be higher than that of TSF[9]. A more recent study examined whether the anthropometric indices are alternatives to npRQ. When the measured values were expressed as percentages of normal values, percent of AMC and percent of AC were found to significantly correlate with npRQ, and a formula using %AC and Child-Pugh scores could represent npRQ[69]. External validation is needed to verify the relationship between the measurement values and

Table 1 Methods to assess protein-energy malnutrition and sarcopenia in liver cirrhosis patients

Method	Ability	Advantage	Disadvantage
PEM			
Indirect calorimetry	To calculate energy expenditure and npRQ npRQ being a marker for survival	Non-invasive and accurate	Expensive
Anthropometric measurements	To estimate nutritional status and liver function AMC and TSF serve as markers for survival %AMC and %AC serve as alternatives to npRQ	Simple and inexpensive	Possible errors related to the measurements
Bioimpedance analysis	To estimate body cell mass PA serves as a measure to estimate nutritional status and as a marker for survival	Convenient and inexpensive Comparable with the DXA and MRI methods in the assessment of skeletal muscle volume	Limitations in patients with ascites
Sarcopenia			
Imaging method	To assess skeletal muscle volume		
CT and MRI		Accurate	Radiation-exposed (CT)
DXA		Comparable with the CT and MRI methods Less radiation exposure and lower cost than the CT method	
Handgrip strength	To measure muscle strength A marker for nutritional status A predictor of hepatic decompensation	Simple and inexpensive	Possible errors related to measurements

PEM: Protein-energy malnutrition; LC: Liver cirrhosis; npRQ: Non-protein respiratory quotient; AMC: Arm muscle circumference; TSF: Triceps skinfold thickness; AC: Arm circumference; PA: Phase angle; DXA: Dual energy X-ray absorptiometry; MRI: Magnetic resonance imaging; CT: Computed tomography.

npRQ. Although anthropometric measurements are simply and inexpensively performed, the interpretation of the measured values should be performed carefully. For example, a study suggested that AMC may be affected by edema[70], a symptom frequently observed in LC patients. Furthermore, possible errors related to anthropometric measurements should be noted: repeated measurements providing different values (unreliability, imprecision, undependability) and measurements departing from true values (inaccuracy, bias)[71].

Bioimpedance analysis

Bioimpedance analysis (BIA) is another measure to assess PEM. This method is based on the measurement of tissue conductivity[72]. Skeletal muscle is a major body component with low resistance and is therefore a dominant conductor[73]. A study with LC patients has demonstrated that BIA is a reliable bedside tool for the estimation of body cell mass, although it is limited in the case of LC with ascites[74]. The phase angle (PA) is a derived measure calculated from two parameters of BIA: PA = arctangent reactance/resistance × 180°/π[75]. Several studies have demonstrated that PA is useful in the assessment of the nutritional status in hemodialysis[76] or preoperative[77] patients. Another study has suggested that PA can serve as a prognostic indicator in cancer patients[78]. With regard to LC, a recent study indicated that PA is a promising parameter for the assessment of patient nutritional status[79]. Furthermore, a study suggested that PA is more predictive of survival than commonly used body composition information: a low PA is associated with shorter survival time[80]. Several studies have revealed that the estimated values of skeletal muscle mass obtained by BIA are not significantly different from those obtained by magnetic resonance imaging (MRI)[73] or dual energy X-ray absorptiometry (DXA)[81] (see below). Because of its convenience and low cost, BIA is a potential alternative to these imaging methods[14].

Methods for sarcopenia assessment

Imaging methods: There are several methods for sarcopenia assessment. Computed tomography (CT) is an imaging method that permits the precise measurement of skeletal muscle volume. CT technology enables specific tissue demarcation according to a CT measure of the tissue, thereby permitting calculation of its area. Human muscle tissue has a CT number in the range of -29 to +150 hounsfield units (HU). Muscles at the third lumbar (L3) vertebra encompass the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. A recent analysis revealed that the calculated L3 muscle area accurately represents the whole-body skeletal muscle volume (r = 0.86-0.94, $P < 0.001$)[82]. Based on that finding, the L3 muscle area normalized for stature (cm^2/m^2) can be used as an index of skeletal muscle volume (the L3 skeletal muscle index, L3 SMI)[65]. Although cutoff values for diagnosing sarcopenia have not been established, a recent study used cutoff values of 38.5 cm^2/m^2 for women and 52.4 cm^2/m^2 for men[65]. MRI has also been used for the assessment of skeletal muscle volume and sarcopenia[73,83,84].

DXA is another imaging method used in sarcopenia assessment. This method allows for the measurement of bone, fat, and lean-tissue content. Appendicular skeletal muscle mass (ASM) accounts for more than 75% of the total body skeletal muscle mass and can thus serve as a marker for sarcopenia[59,85]. ASM divided by height

squared (ASM/Ht^2; kg/m^2)[86] and ASM as a percentage of body weight (ASM/Wt)[87] have been proposed as indices for sarcopenia. Sarcopenia has been defined as an ASM < 1 SD[62] or < 2 SD[59] below the sex-specific mean for a young reference group. The accuracy of the DXA method has been shown to be comparable to that of the CT or MRI method[84,88], and the DXA method requires less radiation exposure and costs than the CT method[88].

Handgrip strength: Decreased muscle strength reflects a decreased volume of skeletal muscle. The European Working Group on Sarcopenia in Older People (EWGSOP) recommends handgrip strength as a practical measure of muscle strength[14]. Handgrip strength has been shown to be a useful marker for the assessment of nutritional status in LC patients[89]. Moreover, a previous analysis has revealed that handgrip strength can be a useful predictor of hepatic decompensation in LC patients[6]. However, it should be noted that considerable variation in the measurement methods has the potential to introduce measurement errors[90].

NUTRITION MANAGEMENT FOR LC PATIENTS

Management for PEM in LC patients

Dietary management: Poor dietary intake is an important cause of PEM in LC patients. In a study of nutritional status in LC patients, decrease in daily caloric intake paralleled worsening of progressive liver failure: 48% and 34% of Child A patients, 51.7% and 35.8% of Child B patients, and 80.3% and 62.9% of Child C patients at admission had a caloric intake below 30 kcal/kg of body weight and protein intakes below 1 g/kg of body weight, respectively ($P < 0.001$). Furthermore, poor dietary intake was found to be an independent predictor for in-hospital mortality[67]. Some studies have aimed to clarify whether efforts to increase dietary intake can improve the outcome of LC patients, and short-term follow-up has suggested an improvement of nutritional status[91,92]. A study of alcoholic LC patients demonstrated that an increase in dietary intake altered the energy metabolism of Child C patients from preferred lipid oxidation to preferred carbohydrate metabolism. However, the dietary management appeared to be limited in improving nutritional status in end-stage LC patients, such as those with refractory ascites[92]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend that energy and protein intake should be 35-40 kcal/kg of body weight per day and 1.2-1.5 g/kg of body weight per day, respectively[93].

The timing of dietary intake can influence energy metabolism. Because LC patients are prone to entering a starvation state after a relatively short fasting period, a large number of small meals ("nibbling" pattern) rather than a small number of large meals ("gorging" pattern) is considered preferable to maintain optimal energy metabolism[94,95]. Several studies of LC patients found that late nocturnal energy supplementation altered energy metabolism from preferred lipid oxidation to preferred carbohydrate metabolism[96,97]. More recently, a randomized controlled trial with LC patients suggested that nocturnal energy supplementation may be superior to daytime energy supplementation for protein accretion[98].

BCAA supplementation: As previously discussed, a lack of BCAAs in LC patients can accelerate muscular protein catabolism, decreased albumin synthesis, and hyperammonemia and associated hepatic encephalopathy. A loss of skeletal muscle volume (*i.e.*, sarcopenia)[16], low serum albumin levels[99-104], and hepatic encephalopathy[105] have been found to be predictors of poor survival in LC patients. These findings lead to the notion that BCAA supplementation may restore impaired protein metabolism and thereby improve outcomes of LC patients. Indeed, previous studies have revealed that BCAA administration stimulates albumin synthesis[40] and protein synthesis in skeletal muscles[106]. Of the BCAAs, leucine[106-108] is considered to play a central role in the synthesis process, of which, the mammalian target of rapamycin (mTOR)[106,107] appears to be a key component in controlling its signaling pathway.

BCAA administration can be conducted either orally or intravenously. A BCAA-enriched amino acid solution has been used in the treatment of acute hepatic encephalopathy for several decades, and its utility has been demonstrated[109]. Oral BCAA-enriched formulas, BCAA granules and BCAA and carbohydrate mixtures, have been used in the effort to achieve preferred nutritional status and improved outcomes of decompensated LC patients[110]. Studies with LC patients have demonstrated that serum albumin levels and npRQ increased with oral BCAA supplementation[111,112]. In a study of HCV-related LC, the intake of BCAA and carbohydrate mixtures as late evening snacks was more effective in increasing serum albumin levels and improving energy metabolism than ordinary food intake[111]. Long-term follow-up studies of BCAA supplementation for LC patients showed positive results. In a randomized clinical trial with decompensated LC patients, supplementation with BCAA granules contributed to preventing progressive liver failure[113]. A similar randomized controlled trial found that supplementation with BCAA granules increased serum albumin levels and contributed to decreased liver failure and mortality[114].

Thus, BCAA supplementation is an effective therapeutic strategy for improving energy metabolism and overall outcomes in LC patients. This nutritional treatment is recommended in several guidelines[93,115]. The optimal timing of BCAA administration during the course of LC remains to be determined, although one randomized controlled trial suggested that patients with a BTR of < 4 should begin BCAA treatment even in cases of compensated LC[116]. Given the close relationship between BCAAs and protein synthesis in skeletal muscles, future studies focusing on the benefits of BCAA supple-

mentation on sarcopenia in LC are necessary. In addition, some evidence suggests that BCAAs are essential for lymphocyte responsiveness and are necessary to support other immune cell functions[117]. Whether BCAA treatment can improve immunity in LC patients with sarcopenia and decrease the incidence of severe infection requires investigation.

Nutrition management of obese LC patients

With the increasing prevalence of obesity worldwide, the prevalence of obese LC patients is increasing[54]. Given that obesity accompanied by LC can accelerate hepatic decompensation[53], enhance hepatocarcinogenesis[118,119], and result in poor patient survival[63,64], nutrition management is imperative for obese LC patients. The restriction of excessive caloric intake without exacerbation of impaired nutrient metabolism is necessary for successful LC management. Furthermore, obesity is closely linked to insulin resistance; this metabolic problem increases the risk of disease progression, hepatocarcinogenesis, and mortality in LC patients[120]. Considering that obesity can exacerbate sarcopenia-associated insulin resistance[62,121], nutrition strategies for insulin resistance appear to be important, particularly in LC patients with sarcopenic obesity. Recent studies have suggested that BCAA supplementation is effective in improving insulin resistance[122,123]. Of the BCAAs, leucine appears to play a critical role in controlling carbohydrate metabolism; the amino acid regulates the oxidative use of glucose by skeletal muscle through the stimulation of glucose recycling *via* the glucose-alanine cycle[122]. Further trials are required to establish dietary regimens, such as dietary nutrient balance, for obese LC patients.

EXERCISE MANAGEMENT FOR LC PATIENTS

Physical activity and exercise capacity in LC patients

A recent survey of LC patients reported that physical activity levels were lower in LC patients than in healthy controls[124]. The survey results also suggested that low levels of physical activity were inversely associated with insulin resistance. In a study of compensated LC, low levels of physical activity and poor caloric intake were closely linked to sarcopenia[125]. These findings indicate that increased physical activity may prevent and improve sarcopenia in LC patients. Indeed, in studies of the elderly[126] or patients with certain types of chronic diseases[127], exercise management has been shown to be effective in preventing and improving sarcopenia.

Exercise capacity is described as the ability to use oxygen during exercise. The commonly used measure of exercise capacity is maximal oxygen consumption (VO_{2max})[128]. Studies with LC patients have shown decreased exercise capacity as evaluated by VO_{2max}[129,130] and an inverse relationship between exercise capacity and the severity of liver disease[130-132]. Recent research has demonstrated that a decrease in exercise capacity is not only associated with LC severity but also predictive of mortality after liver transplantation[133,134]. Earlier studies on exercise management demonstrated that physical training programs as short as approximately one month were useful in increasing VO_{2max} or peak oxygen consumption (VO_{2peak}) in LC patients[131,135].

Given these findings, exercise management is a key component in the management of LC patients because it can lead to increases in physical activity, skeletal muscle volume and strength, and exercise capacity, ultimately improving the quality of life and survival.

Assessment of nutritional status and complications for exercise management

The current guidelines for physical activity and health in older adults (men and women aged $\geqslant$ 65 years and adults aged 50-64 years with clinically significant chronic conditions and/or functional limitations) recommend that moderate-intensity aerobic physical activity should be performed for a minimum of 30 min five days each week in addition to two sessions of resistance training and flexibility exercises each week[136]. The applicability of these recommendations depends on the severity of the chronic conditions and complications. With regard to LC, inappropriate exercise may cause undesirable outcomes due to the impaired energy metabolism and/or complications associated with LC, including ascites[137], hepatic encephalopathy[138], portal hypertension[139], and hepatopulmonary syndrome[140]. For example, in patients with LC, portal pressure and portal hypertension reportedly increased with moderate exercise (30% of the maximum), suggesting that such physical load poses a risk for variceal bleeding[139]. Moreover, exercise under insufficient nutrient intake can promote protein catabolism and thereby a loss of skeletal muscle mass in LC patients[141,142]. The assessment of nutritional status and complications is therefore mandatory before any exercise management of LC patients.

Exercise regimens for LC patients

The optimal exercise regimens for LC patients remain uncertain. However, there are some preliminary data with regard to efficacious exercise management for LC patients. Recently, based on a survey of compensated LC patients, researchers recommended the following exercise regimen: walking 5000 or more steps per day with a total caloric intake of approximately 30 kcal/ideal body weight[125]. The authors claimed that the regimen has the potential to maintain and increase skeletal muscle volume in LC patients. Most recently, a randomized pilot study with LC patients, in which most participants had Child-Pugh grade A LC, examined whether an exercise program combined with leucine supplementation (10 g/d) can improve patient outcome. The program included three sessions per week of a 1-h treadmill and cycle ergometry exercise at an intensity of 60%-70% of the maximum heart rate, over a period of 12 wk. The intervention group had improved exercise capacity, as shown by the 6-min walk test (from

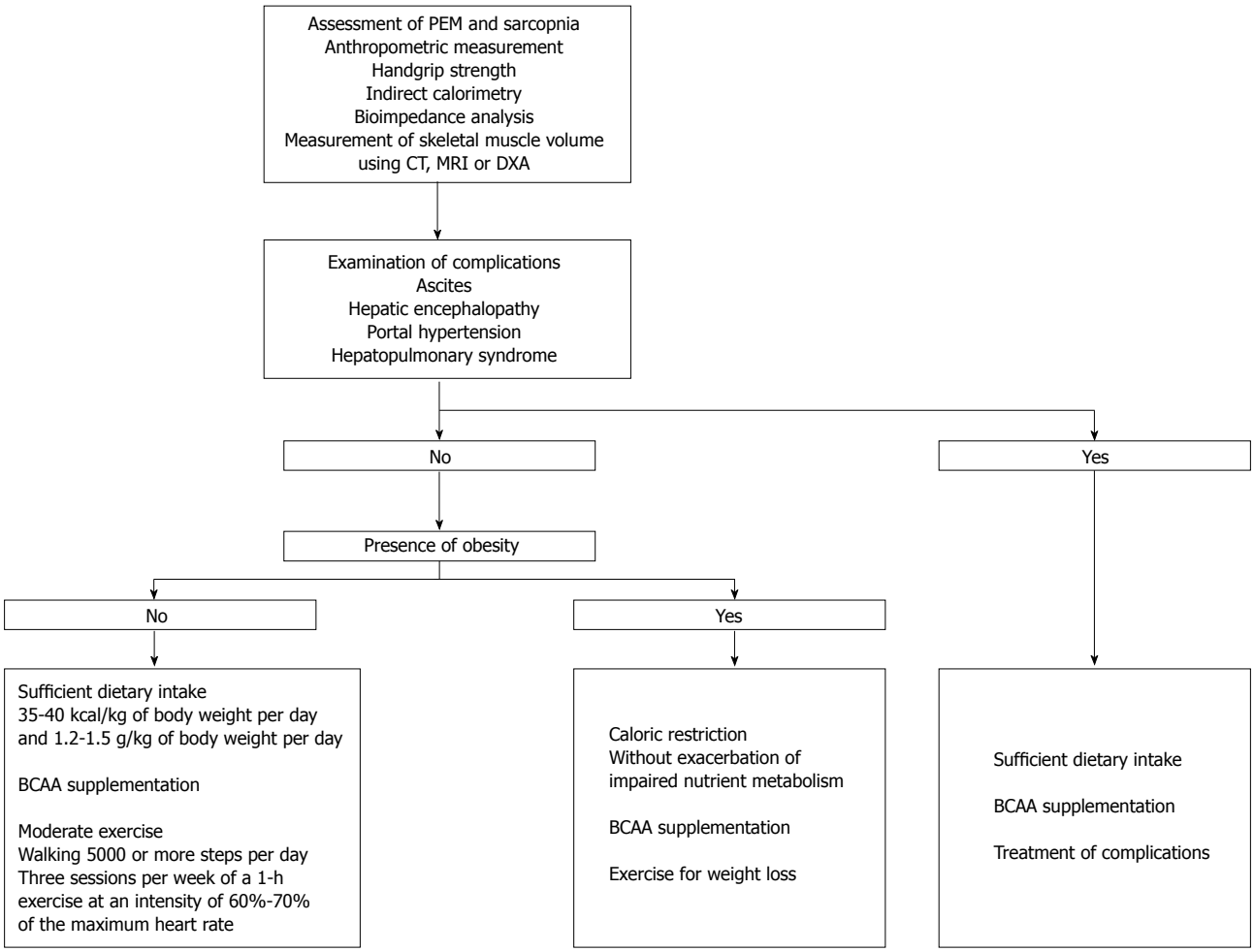

Figure 1 A practical approach for managing liver cirrhosis patients with sarcopenia or sarcopenic obesity. LC: Liver cirrhosis; PEM: Protein-energy malnutrition; CT: Computed tomography; MRI: Magnetic resonance imaging; DXA: Dual energy X-ray absorptiometry; BCAA: Branched chain amino acid.

median 365 m to median 445 m) and the 2-min step test (from median 100 steps to median 150 steps), increased lower thigh circumference, and improved health-related quality of life; the control group had no significant changes[143]. During the study, no adverse events due to the implementation of the exercise program were observed. These studies suggest the possibility that moderate exercise combined with LC-specific nutritional support can increase skeletal muscle volume and improve the outcomes of LC patients. Other studies have indicated that aerobic exercise can be expected to improve insulin resistance in patients with chronic liver disease[144,145]. This favorable effect of exercise on insulin sensitivity is particularly important for obese patients[144,146]. Future intensive studies are required to establish efficacious and safe exercise regimens for LC patients.

CONCLUSION

Substantial data exist clearly demonstrating that PEM confers a risk of poor survival in LC patients. PEM in LC patients is highly associated with sarcopenia and a decrease in serum albumin levels. These conditions have also been reported to be predictors of poor patient survival. Nutrition and exercise management can improve PEM and sarcopenia in LC patients. Nutrition management includes sufficient dietary intake and an improvement of impaired nutrient metabolism. In contrast, the current rise in obesity prevalence has increased the number of obese LC patients. Restriction of excessive caloric intake without exacerbation of impaired nutrient metabolism is necessary for those patients. BCAAs are good candidates for supplemental nutrients for both obese and non-obese LC patients. Exercise management can increase skeletal muscle volume and strength and can improve insulin resistance; however, assessment of nutritional status and LC complications is mandatory before the implementation of an exercise program for LC patients. The establishment of optimal exercise regimens for LC patients is required. Figure 1 shows a tentative practical approach for managing LC patients with sarcopenia or sarcopenic obesity. The further development of methods for nutrition and exercise management will improve the overall health outcomes of LC patients.

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